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Review

Nutrition of preterm infants with bronchopulmonary dysplasia after hospital discharge – Part I

Hercília Guimarães^{1,4}, Gustavo Rocha^{1,4}, M. Beatriz Guedes¹, Paula Guerra², Ana Isabel Silva³, Susana Pissarra^{1,4}

¹NICU, ²Pediatric Division, ³Physical and Rehabilitation Medicine Department Pediatric, Integrated Pediatric Hospital, São João Hospital, ⁴Faculty of Medicine of Porto University, Porto, Portugal

Abstract

Bronchopulmonary dysplasia (BPD) remains the most common severe complication of preterm birth. In addition to well known risk factors, nutrition plays an important role in normal lung development and maturation. Nutrition has a direct effect on the developing lung because it can modulate lung structure. Lung growth and maturation continue after hospital discharge and BPD patient's nutritional requirements and feeding problems will need a specialized multidisciplinary approach during follow-up. Our aim is to review the scientific literature on the most relevant aspects of nutrition of BPD patients after hospital discharge.

Keywords

Preterm infants, bronchopulmonary dysplasia, hospital discharge, nutrition, human milk, formula feeding, undernutrition.

Corresponding author

Hercília Guimarães, NICU, Integrated Pediatric Hospital, São João Hospital, Faculty of Medicine of Porto University, Porto, Portugal; email: herciliaguimaraes@gmail.com.

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Introduction

Bronchopulmonary dysplasia (BPD) is a chronic pulmonary disease that affects mainly preterm infants and remains the most common severe complication of preterm birth. In the past, BPD was mainly caused by ventilator injury and affected about 30% of preterm infants with birth weights below 1,000 grams [1]. The increasing survival of extremely low gestational age (ELGA) infants associated to gentler ventilation techniques, antenatal steroids and surfactant treatment changed the picture of BPD: the so called "new BPD" is a lung development problem with impairment of alveolarisation which results in pulmonary and vascular hypoplasia with less interstitial cellularity and fibrosis [2-4].

Several factors are considered responsible for altering lung development and may subsequently support the development of BPD. In addition to well known risk factors, nutrition plays an important role in normal lung development and maturation [5-8]. Nutrition has a direct effect on the developing lung because it can modulate lung structure. In rats, caloric restriction reduces the alveolar number by 55% and the alveolar surface area by 25% [9]. However, 72 hours after re-feeding rat lungs are remodeled with normal alveolar numbers and surface areas [10].

A sufficient amount of protein and calories is necessary for organ growth; thus, a low protein or caloric intake will impair lung development, resulting in BPD. However, there is an ongoing debate concerning the required amount of nutrients to prevent the postnatal growth retardation or postnatal growth failure also called extrauterine growth restriction (EUGR) of very preterm infants with BPD [11, 12].

Lung growth and maturation continue after hospital discharge and BPD patient's nutritional requirements and feeding problems will need a specialized multidisciplinary approach during follow-up.

Our aim is to review the scientific literature on the most relevant aspects of nutrition of BPD patients after hospital discharge.

Undernutrition, growth failure and nutritional needs in BPD patients

About 50% infants with severe BPD develop postnatal growth failure, defined as weight $< 10^{\text{th}}$ percentile for postmenstrual age (PMA) at NICU discharge [13].

Growth failure is common in infants with BPD, with reported rates of 30% to 67% in infants with BPD and has an impact on growth, persisting in 53% of cases to 4-8 years of age [14-17]. Malnutrition is associated with prematurity and is aggravated by BPD although the actual impact of these two factors is difficult to quantify [18].

During NICU hospitalization preterm infants receive enteral and parenteral nutrition, according to usual recommendations [19]. However, due to the clinical status of high risk newborns, in some severe situations babies receive fewer nutrients that they really need. It has been shown that preterm with BPD received less enteral feeding in the first two weeks of life than those without BPD, suggesting that a minimal amount of enteral nutrition is necessary to prevent BPD [20].

Patients with moderate and severe BPD who already have breathing problems may aggravate their respiratory function during feeding, showing oxygen desaturation that is verified in 6-40% of VLBW infants. This post discharge feeding desaturation also has a negative association with growth outcome in BPD patients [21].

Anorexia often seen in these patients can further aggravate and difficult the oral intake.

The mechanisms of anorexia are probably multiple: exhaustion associated with dyspnoea and respiratory failure (increased effort during breast feeding or bottle feeding), eating disorders (prolonged hospitalizations, divestment in the oropharyngeal sphere, oral painful stimuli) as well as the anorectic effect of pro-inflammatory cytokines. Anorexia may be responsible for oral feeding failure and precipitate the beginning of supplemental enteral nutrition (EN) through a nasogastric tube or gastrostomy.

The behavioural problems can also contribute to an inadequate oral intake (e.g. oral motor dysfunction). Early intervention programs may be helpful in addressing these issues by providing developmental stimulation and physical and occupational therapy as indicated. Referral to a developmental behavioural paediatrician or behavioural psychologist may be helpful for such children.

The inability to meet increased metabolic demands through oral nutrition can be aggravated by the frequent malnutrition and the need for catch up growth. Denne et al. estimated the energy needs of infants with BPD to be 15% to 25% higher than healthy controls [22, 23]. The European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) has recently suggested that a reasonable energy range for healthy growing preterm infants is 110-135 kcal/kg/day, therefore it seems also reasonable to agree that BPD infants may need an even higher caloric intake [19]. Thus, an energy intake of 140 kcal/kg/day can be required during active periods of disease. However

the energy needs can differ from infant to infant and change depending on the patient's respiratory status, clinical condition and level of activity.

Different kinds of oral/enteral feeds are available for preterm babies after hospital discharge: multinutrient fortification of human milk, nutrient enriched formula for preterm infants, postdischarge formula or standard formula for healthy term infants.

Assuming that inferior growth is undesirable we can improve nutrient intake of a human fed preterm infant in two ways: 1) Fortifying expressed breast milk or 2) Replacing some breast feeds with nutrientenriched formula feeds (formula for preterm infants or postdischarge formulae). In this case the effects of the substitution of one third, half, two thirds of daily energy intake in breast-fed infants by formula for preterm infants or postdischarge formula has been studied [24].

Fortified expressed breast milk

Although human milk (HM) is the recommended nutritional source for newborn infants for at least the first six months of life, unfortified HM may not meet the recommended nutritional needs of the growing preterm [25, 26]. Fortification is an alternative approach to increase nutrient intake in human milk-fed infants. It must be started when enteral feed is about 80 ml/kg/day, if the amount of human milk is more than 50% of total enteral feeding. The available human milk fortifiers contain varying amounts of protein, carbohydrate, calcium, phosphate, electrolytes, vitamins and other minerals (zinc, manganese, copper and magnesium) [25]. There are two different forms of fortification of HM: standard and individualized.

The standard fortification consists in adding fixed concentrations of fortifier to maternal milk, not always corresponding to the nutritional requirements of individual infants. This method is commonly used in most NICUs but the results obtained in terms of growth are not always satisfactory. Standard fortification improved short-term growth, increased nitrogen retention, had no long term advantages in terms of either growth or development, had no clear effect on bone mineral content and was not associated with adverse effects [27].

The individualized fortification is now believed to be the best solution to prevent the protein undernutrition of preterm infants. Two methods have been proposed for individualization: targeted fortification, depending on milk analyses, and adjustable fortification, depending on the metabolic response of each infant. Using targeted fortification the amount of fortifier is given according to the weekly determinations of milk protein content. It depends on the availability of the milk analyses [28]. In the adjustable fortification the protein intake is adjusted on the basis of blood urea nitrogen. This method is effective in delivering an adequate protein intake, and growth approximates the one in uterus [29].

For human milk fed infants, either human milk fortification or replacement of some of the feeds (1/3)to 2/3) by preterm or nutrient enriched formulae are, as previously discussed, reasonable alternatives. In this setting, protein, minerals and trace elements are all increased. The strategy to fortify human milk is considerably more laborious and difficult and dispute exists as to which should be the human milk fortifier (formula for term infants, formula for preterm infants or human milk fortifiers used in hospitals). There is some evidence pointing towards a positive relationship between duration of human milk feeding and the later Bayley Mental Index, particularly in infants with chronic lung disease. In a study by O'Connor and co-workers infants with chronic lung disease fed > 50% human milk until term corrected age showed a mean Bayley Motor Index about 11 points higher at 12 months corrected age [30]. There are some concerns regarding safety of fortifying human milk with human milk fortifiers after hospital discharge since the content of some minerals and vitamins may well be excessive, posing these infants at increased risk of trace elements deficiency (copper) and hypervitaminosis (vitamin A and D) [24].

Formula feeding

Postdischarge formulae are specifically designed for preterm infants after discharge from hospital. These are energy (about 72 to 74 kcal/100 ml) and protein (about 1.8 to 1.9 g/100 ml) enriched, and variably enriched with minerals, vitamins, and trace elements compared to standard term formula. Expert bodies and authorities recommend these formulae for preterm infants for three to twelve months post-discharge [31]. Some experts state that current recommendations to prescribe postdischarge formula for preterm infants following hospital discharge are not supported by enough available evidence. However, they agree that some limited evidence exist that feeding preterm infants following hospital discharge with formula for preterm infants (energy enriched [to about 80 kcal/100 ml], protein enriched [2.0 to 2.4 g/100 ml], and variably enriched with minerals, vitamins, and trace elements to support intra-uterine nutrient accretion rates) may increase growth rates up to 18 months corrected age [32]. Healthy preterm babies can up-regulat their feed volume in such away that energy intake is identical no matter the type of milk ingested (human milk, standard, preterm or postdischarge formula) [33]. However same upregulating pattern is difficult for the sick preterm infant with BPD due to the high nutritional needs. It is difficult to provide an adequate caloric intake keeping the amount of fluid in the 130-150 ml/kg/ day range. Infant formulae, designed to be similar to human milk, are typically lower in caloric density, calcium, and phosphorus. Infant formulae (67 kcal/100 ml) and even postdischarge formulae (72-74 kcal/100 ml) would need to be ingested in large volumes of 180-200 ml/kg/day at standard concentrations, if they were intended to meet the energy needs of BPD infants. These difficult infants with BPD usually need concentrated postdischarge formulae (up to 80 kcal/100 ml) or formulae for preterm infants (80 kcal/100 ml) to ensure adequate energy, protein, and mineral intake to promote catch-up weight gain.

We need to be aware that increasing the caloric density of commercial infant formula through concentration or the addition of modular nutrients like glucose polymers and medium chain triglycerides increases the osmolality of the formula, which can cause diarrhoea or malabsorption [34, 35]. For this reason, formulae usually are not concentrated beyond 80 kcal/100 ml unless severe fluid restriction is needed [36]. Additional increases in the caloric density of formulae should be made gradually (e.g. in increments of 3 kcal/30 ml) with modular supplements (glucose polymers, medium chain triglycerides) to a maximum of 100 kcal/ 100 ml. In this setting, the prescriber should be certain that individual nutrients are not provided in excessive amounts. The addition of carbohydrate or fat to infant formulae alters the nutrient ratio of the formula by providing no protein calories [37, 38]. Care should be taken to avoid providing more than 60 percent of energy from fat, which may induce ketosis.

In a study performed by Brunton and co-workers, 60 preterm infants with BPD were randomly assigned to receive, as postdischarge feeding, term or postdischarge formula. The authors reported that BPD infants fed postdischarge formula had higher nitrogen, mineral and zinc retention and, at 3 months corrected age, attained significantly greater length, bone mineral content and lean mass [38]. Fewtrell and co-workers, however, compared high caloric density formula with standard term formula in infants with BPD and found no difference in growth parameters between groups [39].

If the baby has already introduced complementary food, the most caloric solid foods need to be chosen, like soups and dishes enriched with fat and carbohydrates.

How to feed BPD infants to provide nutritional needs in difficult patients?

If despite the optimization of oral intake the child is unable to meet nutritional requirements by mouth in order to achieve adequate catchup growth, supplementation of oral feedings with daytime or nighttime enteric feedings must quickly be considered [37]. Enteral nutrition allows increasing caloric intake, reducing the gastric distension that impairs ventilation and ensures better digestion and intestinal absorption of nutrients. Nasal or orogastric access can be used for infants and children who are predicted to have only short-term need for enteral feeds (e.g. less than two or three months). In addition, they are often used as an interim measure to feed and assess tolerance of enteral feedings before placement of an ostomy for long-term enteral feeding. A soft, flexible feeding tube (e.g. made from polyurethane or silicone) should be used if possible. Tube sizes of 4 French should be used for neonates and infants. Potential disadvantages with this route are interference with oral intake, easy dislodgement, irritation in the nasal/oral area, infection. A gastrostomy tube should be rapidly programmed in the more severe cases or if longterm enteral feeding is required. They are usually easily placed laparoscopically or endoscopically. The gastrostomy can be fitted with a device that is easy to cover with clothes and transient and easily removed without sequelae when no longer needed. Disadvantages of gastrostomy placement include local irritation/infection, leaking, allergic reaction, and possible dislodgement. The appropriated formula for enteral feeding could be the human breast milk or preterm formula or postdischarge formula, eventually concentrated and/or enriched until 1 kcal/ml. Bolus intragastric feedings are generally preferred over continuous feeds if they can be tolerated, since they provide a more normal pattern of eating and can deliver larger volumes over a shorter period of time (generally 10 to 30) minutes per bolus). If the patient can tolerate a bolus by gravity infusion, a pump is not necessary. Bolus feeds may also reduce the risk of aspiration because they are typically administered while the infant or child is awake and upright. On the other hand, the bolus feeding method might also increase the risk of pulmonary aspiration if large volumes are given. If a bolus feed is given while the child is asleep, the head of the bed should be elevated at least to a 45 degree angle to help reduce aspiration risk [40]. All patients undergoing a nutritional program of oral/enteral feeding should be strictly monitored and energy intake must be adjusted as required. They need to be periodically reassessed by plotting serial heights and weights, and the volume, concentration and type of feeds should be adjusted to achieve optimal growth.

In conclusion, successful management of difficult infants with BPD and failure to thrive (undernutrition) would benefit from comprehensive postdischarge nutrition that should require a plan to address contributing medical, nutritional, developmental/behavioural, and psychosocial factors. That includes the use of nutrient-enriched preterm/postdischarge formulae, eventually concentrated and enriched into 1 kcal/ml and also the use of enteral nutrition and feeding therapy, ensuring adequate energy intake, parental support and education.

Vitamins and mineral supplementation

Whilst a considerable attention has been focused on preterm macronutrient needs after discharge, less attention has been placed on micronutrients, in particular minerals, trace elements and vitamins.

Calcium and phosphorus are of major concern in preterm babies since these elements are accreted primarily in the third trimester of pregnancy and it is very difficult to ensure an adequate dietary supply of these minerals during the first few weeks of life, particularly in the smallest and sickest of these babies, conditioning the occurrence of undermineralized bones. Infants with BPD are at increased risk of calcium and phosphorus deficiency due to their low enteral intakes associated with fluid restriction and the common need for diuretic therapy [14, 41]. The Nutrition Committee of the ESPGHAN recommends an intake of 120-140 mg/ kg/day of highly bioavailable calcium salts and 60-90 mg/kg/day of phosphate [19]. It is likely that when a mineral rich postdischarge or preterm

formula or fortified human milk is used, no extra mineral supplementation, namely of calcium and phosphorus, is needed [42, 43].

Iron supplementation need depends on feeding regimen (human milk versus nutrient enriched or preterm formula) and history of previous multiple transfusions of packed red blood cells. Different scientific societies agree on the need for iron supplementation of preterm infants with 2 mg/kg/ day until 12 months, amount already provided by fortified formulae. Patients submitted to multiple packed red blood cell transfusions probably don't need iron supplementation [19].

Vitamin D, glucocorticoid and retinoid are involved in the alveolarization. Knowing that BPD is characterized by arrested alveolarization, a complex integration of their effects on gene expression in postnatal lungs seems to contribute to the improvement of alveolarization [44].

There is no evidence that preterm infants after discharge should receive greater doses of vitamin D than term infants. However, the Nutrition Committee of the ESPGHAN suggests an intake of 800-1,000 IU/day of vitamin D [19].

The administration of vitamin A, necessary for proper development and healing of lungs, has been reported on BPD prevention, but there are no studies about its effect on BPD discharged patients [45].

Declaration of interest

The Authors declare that there is no conflict of interest.

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